PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

FROM QUALITATIVE TO QUANTITATIVE BENEFIT-RISK DECISION-MAKING:
STRUCTURED BENEFIT-RISK ASSESSMENT

IMI-PROTECT Symposium

Benefit-Risk Integration and Representation Workshop

18th February 2015

Richard Nixon, PhD

Disclaimer

"The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines.

This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency."

PROTECT is receiving funding from the European Community's Seventh Framework Programme (F7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu)

Decide on a Multiple Sclerosis treatment

Three outcomes are important to you

- For two treatments given over a two-year period the proportion of patients experiencing each of three outcomes is:

	Treatment A	Treatment B
Disability progression	40%	30%
Flu-like reaction	5%	3%
PML*	0%	0.5%

- Which treatment would you choose?
  - How often does each outcome occur?
  - How important is each outcome if it occurs?
- In real life the decision is more complex
  - Which **outcomes** do you choose to make the decision?
  - Which **treatments** do you choose between?
  - How do you assess how **important** each outcome is to you?

* PML: Progressive multifocal leukoencephalopathy

Natalizumab – A short history

- Natalizumab was approved in 2004 by the FDA for the treatment of relapsing remitting multiple sclerosis (RRMS).
- In 2005 the drug was suspended because of an associated incidence of progressive multifocal leukoencephalopathy (PML), a rare neurological disorder.
- In 2006 it was re-introduced due to patient demand, but with strict risk minimization measures.
- In 2009, due to occurrence of further PML in monotherapy post marketing, CHMP reassessed the PML risk of Tysabri and confirmed the current approval.

The BRAT* Framework for benefit-risk

Built on methods to support decision making

- **A framework, not a recipe**
  - A tool to support decision makers, not an algorithm to replace them.
  - Helps to develop a common understanding of that is of central importance.
  - Process to structure and analyze information.
  - Visualization tools to communicate benefit-risk.
- **Built on well-established Decision Analysis principles**
  - Promotes traceability, transparency and consistency.
- **Communication tool for decision making**
  - Consolidated view of key benefit and risk outcome measures.

*Benefit Risk Action Team

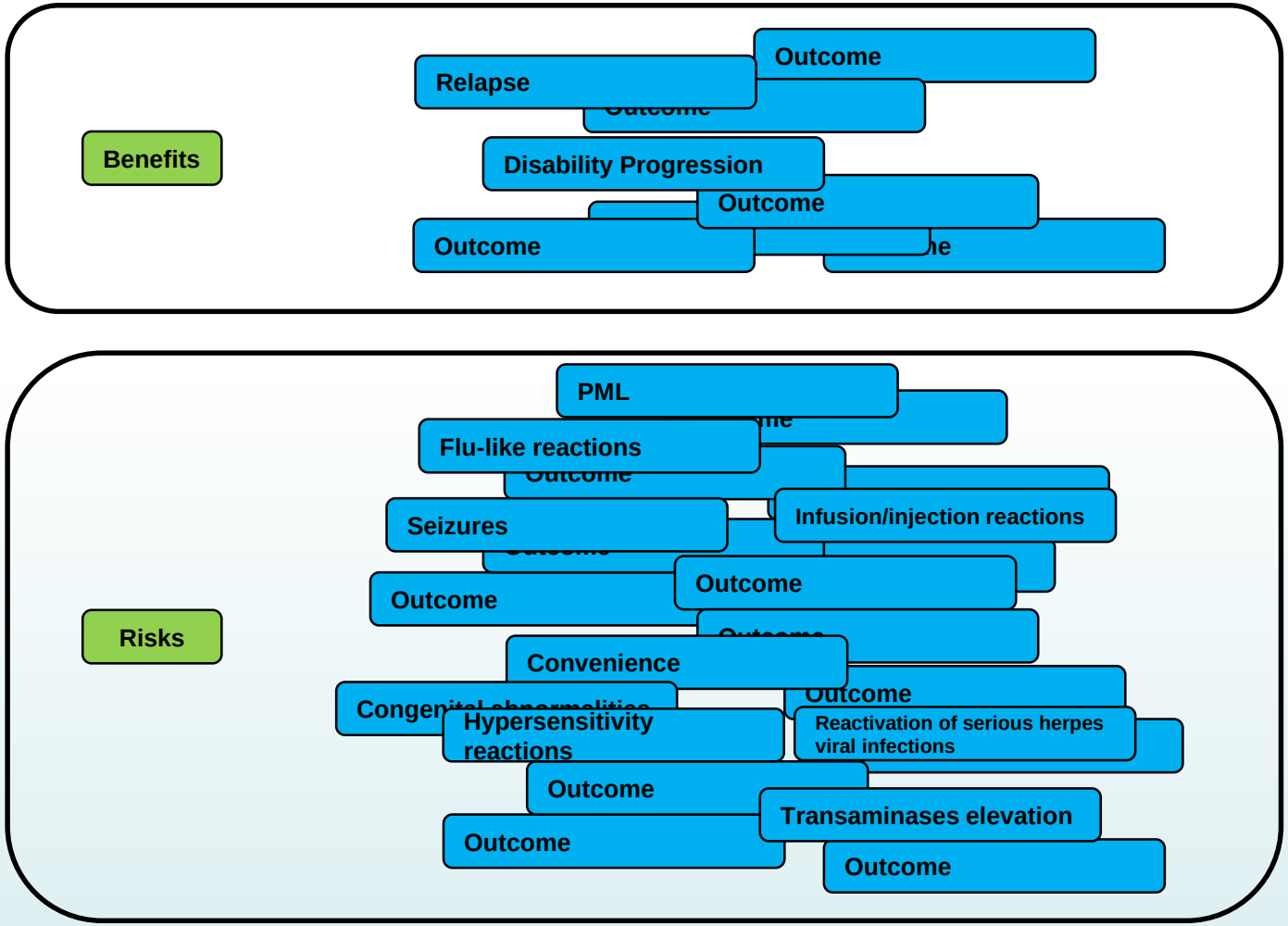
1) Define a decision context

Sets the frame of the structured benefit-risk assessment

Objective	**Should natalizumab be kept on the market given that episodes of PML are observed?**
Indication	**Relapsing remitting multiple sclerosis**
Population	**Adults with relapsing remitting multiple sclerosis**
Drug	**Natalizumab, 300mcg, iv, qm.**
Comparative Treatment Alternative(s)	**Placebo, Interferon beta-1a, 30mcg, im, qw Glatiramer acetate, 20mg, sc, qd**
Assessment time point	**Two years. For PML fives year as it takes longer to manifest.**
Stakeholder perspective	**EMA**

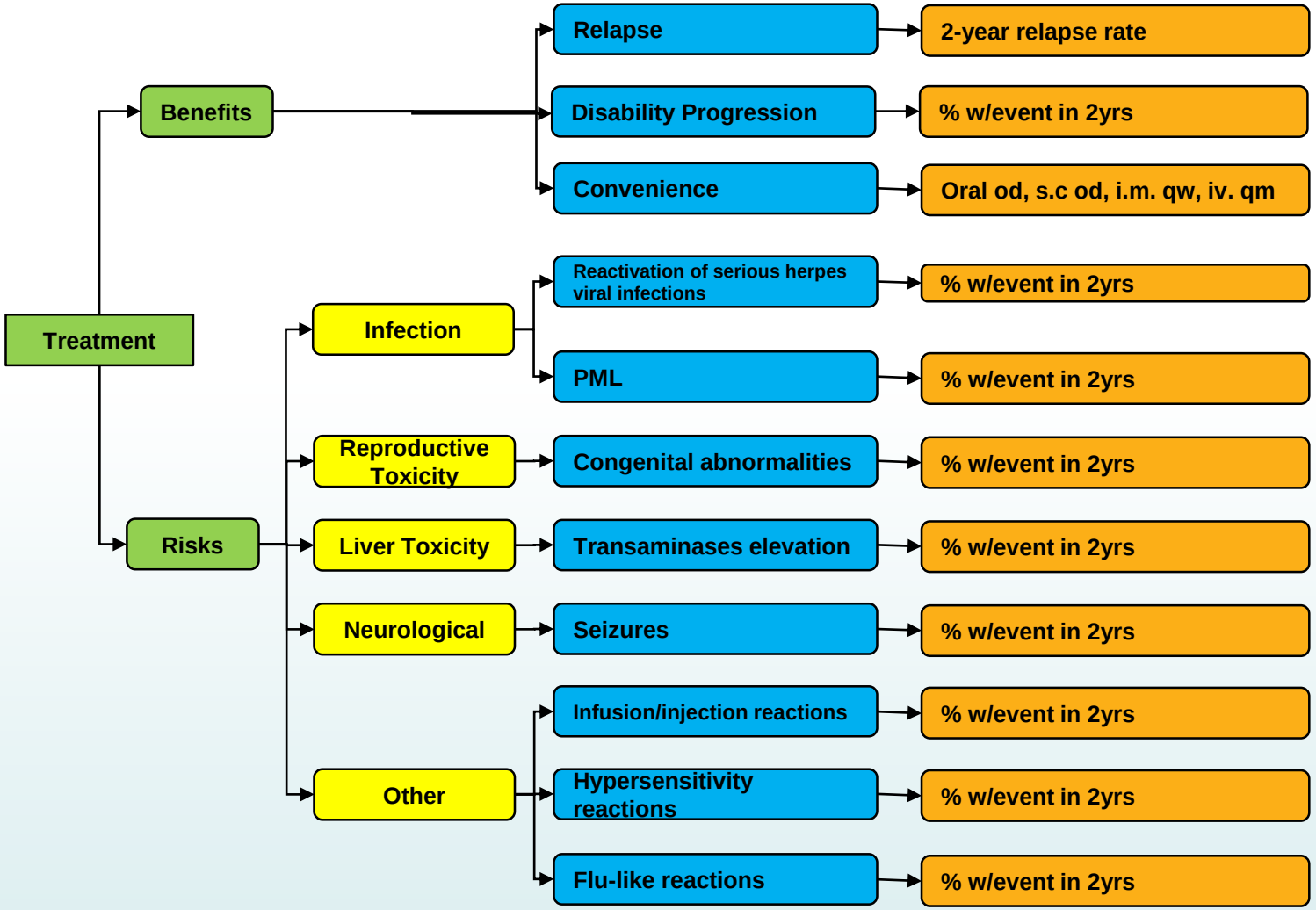
2) Identify key benefits and risks

Organize the key outcomes driving the benefit-risk in a value tree



2) Identify key benefits and risks

Organize the key outcomes driving the benefit-risk in a value tree



3) Consolidate source data

Pool clinical data from internal and external studies

Identify

Search strategy

Search query

PubMed.gov
US National Library of Medicine
National Institutes of Health

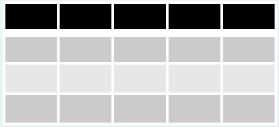
Drugs@FDA
FDA Approved Drug Products

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Select

Study eligibility criteria

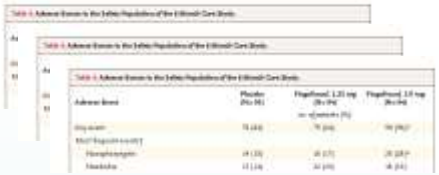
Study worksheet



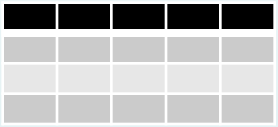
one row per study

Extract

Extraction guidelines



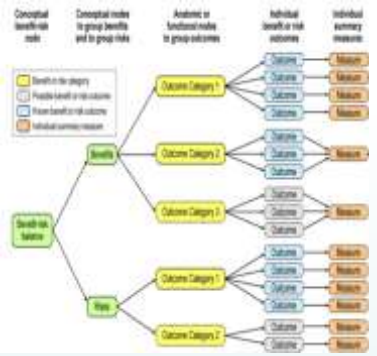
Data source table



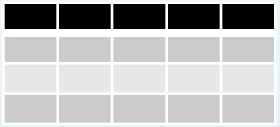
one row per study/treatment/outcome

Aggregate

e.g. meta-analysis, placebo-calibration



Data summary table



one row per outcome

4) Customize and communicate

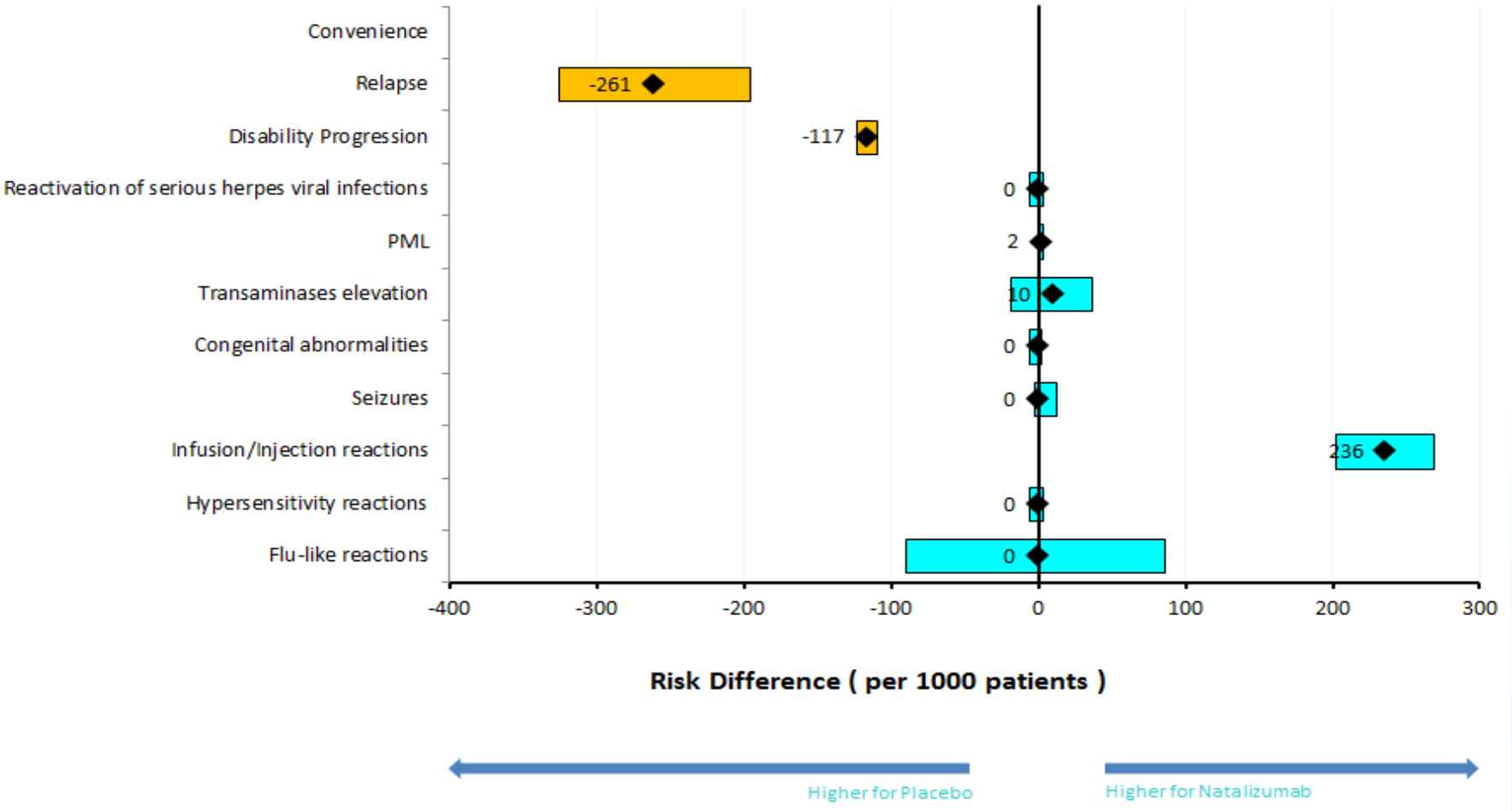
Effects table of key benefits and risks

		Outcome	Natalizumab prob / 1000pts	Placebo prob / 1000pts	Prob difference (95%CI) / 1000pts	
Benefits	Convenience Benefits	Convenience	-	-	-	(-,-)
	Medical Benefits	Relapse (# patients)	276	537	-261	(-326,-195)
		Disability Progression	113	230	-117	(-124,-110)
Risks	Infection	Reactivation of serious herpes viral infections	0	0	0	(-6,3)
		PML	1.51	0	1.51	(0,3)
	Liver Toxicity	Transaminases elevation	50	40	10	(-19,36)
	Reproductive Toxicity	Congenital abnormalities	0	0	0	(-6,3)
	Neurological Disorders	Seizures	5	5	0	(-2,12)
	Other	Infusion/Injection reactions	236	0	236	(202,269)
		Hypersensitivity reactions	0	0	0	(-6,3)
		Flu-like reactions	399	399	0	(-90,86)

Summarize in one place all the benefits and risks data that are driving the decision

4) Customize and communicate

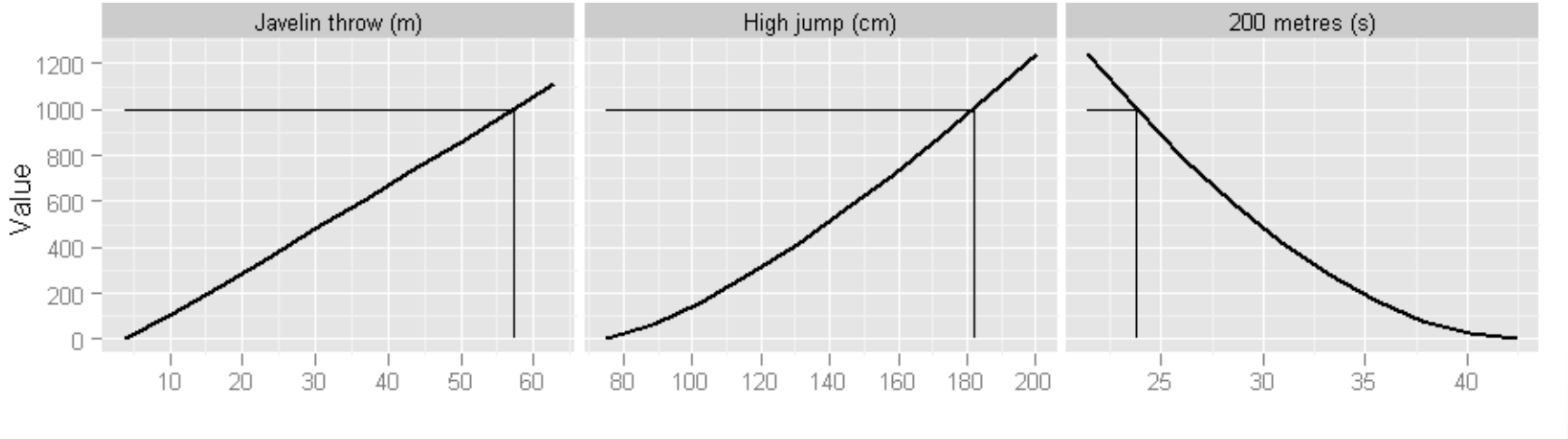
Forest plot



Relapse = Number of patient with at least one relapse

5) Assess outcome importance

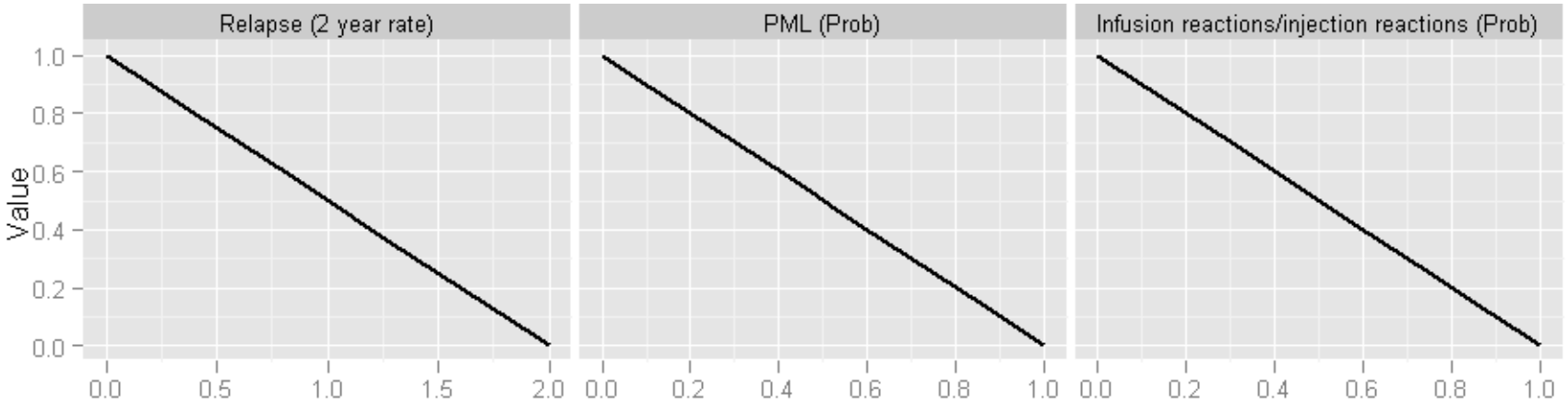
MCDA and the Women's heptathlon



Event	Jessica Ennis	Value	Lilli Schwarzkopf	Value	Tatyana Chernova	Value
Javelin throw (m)	47.49	812	51.73	894	46.29	789
High Jump (cm)	186	1055	183	1016	180	979
200 metres (s)	22.83	1096	24.77	909	23.67	1013
Total		**2963**		**2819**		**2781**

5) Assess outcome importance

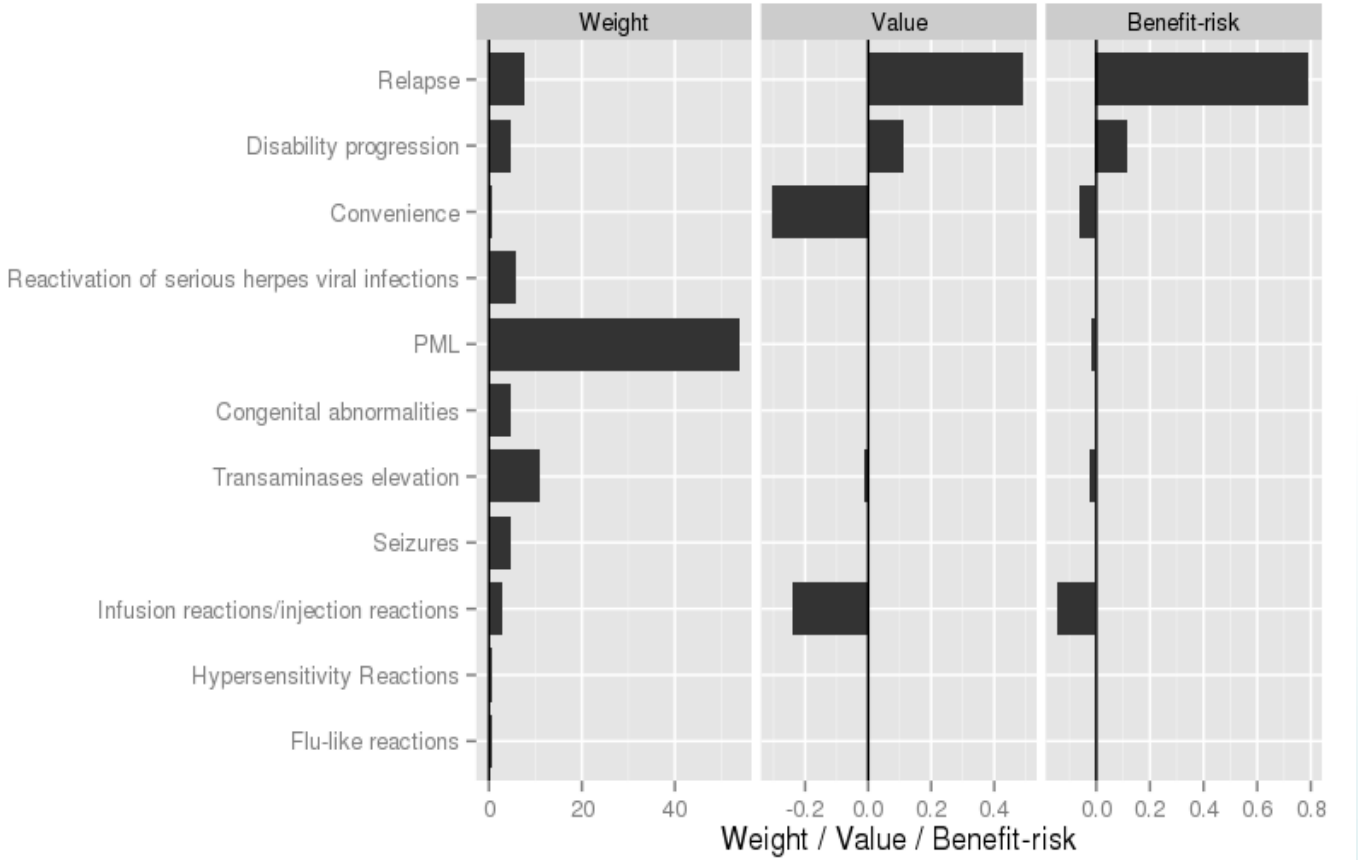
MCDA and multiple sclerosis drugs



		Placebo			Natalizumab		
Outcome	**Weight**	**Measure**	**Value**	**Benefit-risk**	**Measure**	**Value**	**Benefit-risk**
Relapse	8%	1.46	0.27	0.022	0.47	0.766	0.061
PML	54%	0	1	0.54	0.0015	0.998	0.54
Infusion reactions injection reactions	3%	0	1	0.03	0.24	0.764	0.02
Total				**0.59**			**0.62**

Drill down to the values and the weights

Incremental benefit-risk of natalizumab – placebo



This shows which outcomes are contributing most to the total benefit-risk.

Even though the weight given to PML is large, the incidence is small, leading to a small contribution to the benefit-risk.

Waterfall plot

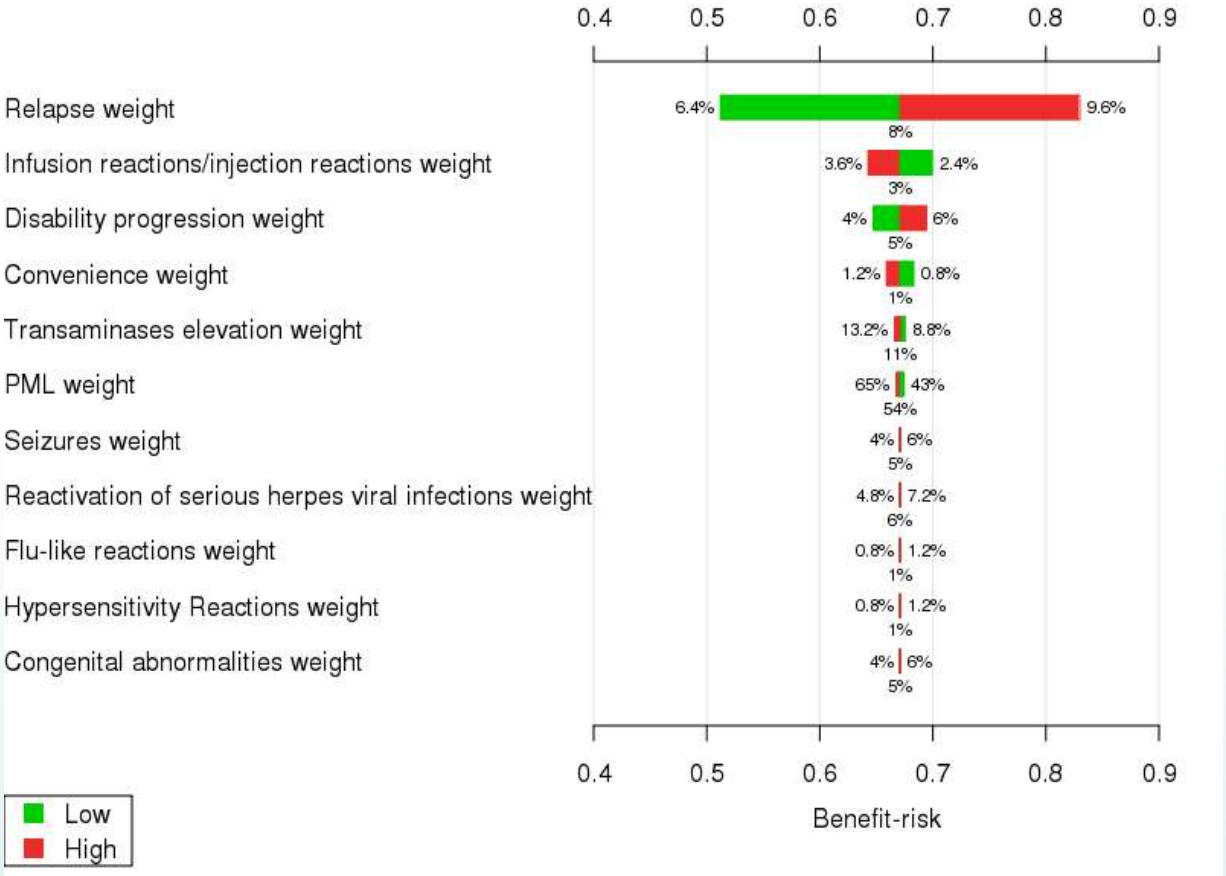
Incremental benefit-risk of natalizumab – placebo

Outcome

- The length of each bar gives the contribution to the overall BR.
- End of the last bar gives the overall benefit-risk.
  - Denominated in the BR of one EDSS progression
- Green = positive BR.
- Red = negative BR.
- The contribution to the overall BR of PML is very small.

Sensitivity analysis on the weights

Incremental benefit-risk of natalizumab – placebo



- The weights are shown under each bar.
  - The base case weight is shown in the middle, with a +/- 20% range given at the ends.
- The weights are changed one at a time.
- The most important weight is the one given to relapses.

Current vs. future benefit-risk communication

From a narrative to a structured framework

"Traditional" benefit-risk communication

- Narrative describing benefits and risks.
- Lacking explicit identification of **key** benefit and **key** risk outcomes.
- Limited systematic comparison of active drug vs. comparators for all key benefits and key risks.
- No structured, quantitative summary of all key benefit and key risk outcomes.

Structured benefit-risk leads to communication that is transparent and defensible

- Which key benefits and key risks were considered and why.
- Which comparators were chosen.
- The magnitude of benefit and risk effects.
- Presentation in a graphical/tabular summary together with concise text.
- Written in such a way as to meet the Health Authority reviewer needs and expectations.

Acknowledgements and further details: Special issue of the Biometrical Journal

Biometrical Journal **00** (2015) 0, 1–20 DOI: 10.1002/bimj.201300248 1

A case study using the PrOACT-URL and BRAT frameworks for structured benefit risk assessment

Richard Nixon[*,**,1], **Christoph Dierig**[2], **Shahrul Mt-Isa**[3], **Isabelle Stöckert**[2], **Thaison Tong**[4], **Silvia Kuhls**[2], **Gemma Hodgson**[5], **John Pears**[6], **Ed Waddingham**[3], **Kimberley Hockley**[3], and **Andrew Thomson**[7]

[1] Novartis Pharma AG, Statistical Methodology and Consulting, CH-4002 Basel, Switzerland
[2] Bayer Pharma AG, Global Development, D-42096 Wuppertal, Germany
[3] School of Public Health, Imperial College London, St. Mary's Campus, Norfolk Place, London W2 1PG, UK
[4] Health Economics and Decision Science (HEDS), School of Health and Related Research (ScHARR), University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK
[5] Qi Statistics, Penhales House, Ruscombe, Berkshire RG10 9JN, UK
[6] Astra Zeneca, R&D Global Regulatory Affairs, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK
[7] Vigilance & Risk Management of Medicines Division, Medicine and Healthcare Products Regulatory Agency, 151 Buckingham Palace Road, London SW1W 9SZ

ACKNOWLEDGEMENT

Support

- The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency.

- The PROTECT project has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

IMI-PROTECT Benefit-Risk Group

Deborah Ashby, Alain Micaleff, Steve Hobbiger, Ioanna Tzoulaki, Diana Hughes, Shahrul Mt-Isa.

Billy Amzal,Simon Ashworth, Alex Asiimwe, Johan Bring, Torbjorn Callreus, Edmond Kakit Chan, Christoph Dierig, Gerald Downey, David Gelb, Georgy Genov, Alesia Goginsky, Christine Hallgreen, Richard Hermann, Ian Hirsch, Kimberley Hockley, Gemma Hodgson, Juhaeri Juhaeri, Silvia Kuhls, Alfons Lieftucht, Alison Lightbourne, Davide Luciani, Marilyn Metcalf, Jeremiah Mwangi, Thai Son Tong Nguyen, Richard Nixon, Rebecca Noel, John Pears, Ruth Peters, Lawrence Phillips, George Quartey, Sinan B. Sarac, Susan Shepherd, Isabelle Stoeckert, Elizabeth J. Swain, Andrew Thomson, Laurence Titeux, Rianne van den Ham, Tjeerd van Staa, Edward Waddingham, Nan Wang, Lesley Wise.

Subhakanta Das, Jane Okwesa, Emily Thompson.